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EXAMINER
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ART UNIT	PAPER NUMBER
1648	

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11

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	10/056,052	PATTI ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *18,20-22 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,19,23,24 and 26-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Groups I, B, H4 and L4 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the Applicants have amended the application such that a linking claim is present, and because the different antigens of (A)-(C) (CLf33, Clf40, and Clf N3) pertain to different fragments of the same protein. These arguments are not found persuasive.

First, the presence of a linking claim does not negate the restriction requirement. Under USPTO linking claim practice, the restriction may still be required, but the linking claim will be examined along with the elected invention. See, MPEP § 809.03. If upon examination, no substantive rejection is found for the linking claim, the restriction among the Groups it comprises will be withdrawn.

Second, the fact that the different polypeptide targets of the claimed antibodies are from the same protein does not demonstrate that the restriction among antibodies that target the different regions is improper. With respect to each antibody, the Examiner must conduct a separate search for antibodies that target the particular regions of the protein. A reference that teaches one of the claimed antibodies need not necessarily provide any information pertaining to the patentability of the others. Because a separate search is required for each of the groups, and because the antibodies of the separate groups performs a different function (binds a different protein sequence) the restriction is still deemed proper.

It is noted that claims 23 and 24 are linking claims to the Clf33 and Clf N3 regions of the protein. Because antibodies that bind the Clf40 region encompass the elected antibodies, such will be examined, claim 23 and 24 will be examined to the extent they read on the elected invention.

In view of the above, the restriction is still deemed proper, and is therefore made FINAL.

2. Claims 18, 20-22, and 25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Sequence Rules Compliance

3. **(Prior Objection- Maintained)** The specification and claims 27-31 were objected to in the Restriction Requirement for referring to protein or nucleic acid sequences without also identifying them by the sequence identifier assigned to them in the sequence listing as required by 37 CFR 1.821(d). Applicant's amendment of the claims and specification corrected most of the errors. However, the nucleic acid encoding the variable light chain of the antibody 35-006 (pages 38-39) has not been amended such that it identifies the sequence by its Sequence Identifier. The objection is therefore maintained.

Claim Objections

4. Claim 1 is objected to because of the following informalities: the claim refers to the Staphylococcus aureus clumping factor A protein by its acronym (ClfA) without first identifying the protein by its complete name. Appropriate correction is required.

5. Claim 8 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This claim describes the antibody of claim 1 comprising an antibody fragment "having the same binding specificity of an antibody which binds to" the ClfA protein. Claim 1 describes an antibody that binds to the ClfA protein. As the antibodies of claim 1 would inherently comprise the fragments specified in claim 8, claim 8 is not further limiting of claim 1.

6. Claim 28 is objected to because of the following informalities: It appears as though the claim should read on an antibody "wherein the variable *light* chain" comprises SEQ ID NO: 27, rather than a "variable *heavy* chain." See SEQ ID NO: 18, disclosing a variable light chain, and comprising SEQ ID NO: 27. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 11-14, 27-31, and 33-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to any antibody that bind to the ClfA protein, and that

comprises, the variable heavy (VH) chain of SEQ ID NO: 20, the variable light (VL) chain of SEQ ID NO: 18, or the amino residues of SEQ ID NOs: 25, 26, 28, or 29 (each representing a CDR from either the VH or VL chains). Each of these claims is drawn to a genus of antibodies, wherein the antibodies have a particular function, and comprise a particular sequence.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed. It is noted that the Applicant has provided several examples each of antibodies with certain of the disclosed sequences (see Figure 8), and antibodies capable of binding to a ClfA protein.

However, while the Applicant has shown that subsets of antibodies that is capable of binding ClfA have the disclosed sequences, and that some antibodies with the disclosed sequences bind ClfA, the Applicant has not shown that every antibody with the claimed sequences is capable of binding to ClfA. See e.g., Monestier, J Immunol 152: 667-75, at 667, and

page 671, figure 4 (disclosing murine anti-Ag autoantibodies comprising the residues of SEQ ID NOs: 25 and 26); Tempest et al. WO 94/10332, page 2, lines 16-23, and figure 2 (disclosing antibodies with the sequences of SEQ ID NO: 28, and a sequence varying from SEQ ID NO: 29 by one residue); and Tillman et al., J Exp Med 176: 761-79, at 768 (disclosing an anti-murine DNA antibody with a variable light chain comprising each of SEQ ID NOs: 27-29). Thus, while the Applicant has provided examples, these examples do not enable those in the art to distinguish the claimed antibodies from other antibodies in the art. I.e., because the art demonstrates that antibodies comprising these CDRs have binding specificity for other molecules that ClfA, the limitation of the claims to the CDR sequences is not sufficient to demonstrate possession any antibody that binds ClfA comprising these sequences. Thus, the working examples alone do not satisfy the written description requirement.

In the claims, the Applicant has identified the antibodies with a combination of function and structure. However, as indicated in the Monestier, Tempest, and Tillman references, antibodies with the disclosed sequences, or with sequences nearly identical to them, have been shown to bind to proteins other then ClfA. Thus, it is clear that the presence of any one of the identified sequences alone does not demonstrate that an antibody has the desired binding property (i.e. there is no correlation between the structure and function). Because the Applicant has not demonstrated a correlation between the claimed structures and the desired function the Applicant has not provided sufficient written description support for the claimed classes of anti-ClfA antibodies.

Furthermore, while the Applicant has demonstrated that antibodies comprising all of the disclosed CDRs, and both of the claimed variable chains comprising them, the Applicant has not

provided any written description for any antibodies that comprise either only one of the two chains, or that comprise only one of the disclosed CDRs. Because, as indicated above, the Applicant has not demonstrated that any antibody comprising any one of the CDRs is capable of binding to ClfA, or that any antibody that comprises only the disclosed VH chain, or the disclosed VL chain, but not both, would be capable of binding to ClfA, the Applicant has not demonstrated possession of the generic inventions encompassed by these claims.

Claim 29 describes an antibody comprising a variable heavy chain CDR1 region comprising SEQ ID NO: 27. However, no such antibody has been disclosed by the Applicant. Rather, the specification identifies this sequence as a CDR1 region of a variable light chain. However, as described above, even were the claim amended to read on an antibody with the CIDR1 light chain comprising SEQ ID NO: 27, this claim would also be rejected for the same reasons as indicated above with regards to claims 27 and 28.

9. Claims 11-14, 26-31, and 33-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an anti-ClfA antibody comprising the VH region of SEQ ID NO: 20, and the VL region of SEQ ID NO: 18, does not reasonably provide enablement for any anti-ClfA antibody comprising fewer than all of the CDRs of SEQ ID NOs: 25-29 as disclosed in the chains of SEQ ID NOs: 18 and 20. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The claims have been described above.

The Applicant has provided several working examples of antibodies that bind to ClfA. However, while the Applicant has demonstrated that the disclosed CDRs are part of anti-ClfA antibodies, the Applicant has not established that any one of the CDRs, or either of the variable chains alone, is responsible for determining the specificity of the claimed antibodies. However, while the Applicants teachings regarding specific ClfA binding antibodies is limited, the scope of the claims is quite broad. They read on any antibody that binds to ClfA comprising one of the disclosed CDRs. No guidance has been provided by the Applicant as to what other antibody variable chain sequences comprising these CDRs would result in an antibody capable of binding to ClfA.

The art recognizes that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity that is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 79:

1979). Rudikoff et al. teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Further, as indicated by each of Monestier, Tempest, and Tillman, the presence of one of the disclosed CDRs does not demonstrate ClfA binding specificity. Each of these references discloses that antibodies comprising at least two of these CDRs may have binding affinities for molecules other than ClfA. Tillman in particular demonstrates a VL chain comprising each of the CDR of SEQ ID NO: 18, and varying from SEQ ID NO: 18 by only 7amino residues, which has a binding affinity for a completely different form of molecule from ClfA. Thus, the art demonstrates that the entire sequence of the antibody variable chain regions comes into play in the determination of antibody binding specificity.

From the above, it is clear from the art that antibody binding specificity is highly dependant on the sequence of the variable heavy and light chains. The Applicant has not shown that antibodies comprising less than both of SEQ ID NOs: 18 and 20 would be capable of binding to the ClfA protein, or provided any evidence that, in this particular case, the general rule does not apply. In view of this, the Applicant is not enabled for any anti-ClfA antibodies comprising SEQ ID NOs: 18, 20, or 25-29 individually, or in any other conformation other than as an antibody comprising both the VH chain of SEQ ID NO: 20, and the VL chain of SEQ ID NO: 18.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-10, 15, 19, 23, 24, 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al., U.S. Patent 6,008,341. These claims read on monoclonal antibodies that bind to the ClfA protein, and more specifically, to embodiments wherein the antibodies bind to the Clf33 region of the protein (comprising residues 221-550 of the ClfA protein). Foster discloses the making of polyclonal antibodies to the identified polypeptide. See, columns 7-8. Further, the reference also teaches that the region of the protein that appeared to encompass the active site of the protein was from residue 221 to residue 550. Id., at col. 8, lines 23-24. Cf., Application, page 19, (disclosing that the Clf33 region of ClfA comprises residues 221-550 of the ClfA protein). The reference also teaches that both polyclonal and monoclonal antibodies raised against the fibrinogen binding domain of the polypeptide (therefore the polypeptide of residues 221-550) could be used for passive immunization by intravenous injection against the S. aureus infection. Thus, the reference provides a suggestion for, and renders obvious the making of antibodies to the Clf33 region of the CLFA protein.

It is noted that, while the reference does not actually teach the making of monoclonal antibodies to the identified protein region, methods of making such antibodies would have been apparent to those in the art in view of the suggestion by Foster to do so. See e.g., Kohler et al., Nature 256: 495-98, and page 6, lines 2-26 (respectively teaching a method of making such monoclonal antibodies, and stating that methods of making of such antibodies is well known in the art). Because the Applicant has indicated that the method of Kohler is well known in the art,

it would also have been obvious to make murine anti-ClfA antibodies as taught by that reference. The Foster reference therefore renders obvious the claims to the monoclonal antibodies. Because the reference also teaches that such antibodies may be administered intravenously for the treatment of (vaccination against) S. aureus infection, the reference also renders claim 5 obvious.

Further, the reference also teaches that the fibrinogen binding is important to the initiation of infection (columns 1-2), and teaches that the clumping factor protein (ClfA) of S. aureus is the fibrinogen binding protein of that organism (col. 1, lines 6-10, and col. 2,lines 42-46). Thus, the reference indicates that certain antibodies to these proteins would be able to both inhibit bacterial binding to fibrinogen or fibrin, and thereby inhibit bacterial infection. Thus, the reference renders claims 3 and 4 obvious.

Finally, the reference teaches that the ClfA protein to which the disclosed antibodies bind have the sequence of the patent's SEQ ID NO: 2. See, cols. 5-6. This ClfA protein comprises the Clf33 polypeptide of SEQ ID NO: 4 of the current application. Thus, the antibodies taught by the reference would bind to the sequence of SEQ ID NO: 4, and to the sequence of SEQ ID NO: 2 of the present application which comprises SEQ ID NO: 4.

12. Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster as applied to claim 1 above, and further in view of Na et al., Clin Diagn Lab Immunol 6(6): 924-29. Claims 16 and 17 are drawn to diagnostic kits comprising the claimed antibodies, and to kits wherein the antibodies are linked to a detectable label. Foster teaches that the anti-ClfA antibodies may be used in the diagnosis of S. aureus infection. Col. 11, lines 24-26. However, the reference does not teach the linking of the antibodies to a detectable label.

Na teaches the use of ELISA to detect pathogenic antigens. See, abstract. Thus, it would have been obvious to those in the art to have used the antibodies of Foster in such an ELISA assay for S. aureus antigens. Because this assay detects antibodies through linkage of the antibodies to a detectable label, the combined teachings of Foster and the art render the claims obvious.

13. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Foster as applied to claim 1 above, and further in view Sieradzki et al. (J Antimicrob Chemother 39 (Supp. A): 47-51). This claim reads on a composition comprising the claimed anti-ClfA antibody and an antibiotic. Foster teaches that the antibody may be used as a treatment against S. aureus infection. Cols. 10-11. However, the reference does not teach the combination of the antibody with an antibiotic.

Sieradzki teaches several antibiotics that are effective against S. aureus, and further indicates that "it is conceivable that a combination of antibacterial agents with different modes of action would be useful against some [antibiotic resistant] strains." Page 47. It is known in the art that antibodies have a different mode of operation from antibiotics. See e.g. Nilsson et al., J Clin Invest 101: 2640-49. Because Sieradzki suggests the combination of antibacterial agents with different mechanisms of action, and because the antibodies of Foster have a different mechanism of action from the antibiotics of Sieradzki, it would have been obvious to those in the art to have combined the antibodies of Foster with an antibiotic to improve the antibacterial effects of the two compositions.

Further, because the art teaches that antibiotics against the bacteria are known and because Foster discloses that the anti-ClfA antibodies are useful in the treatment of S. aureus infection, it would also have been prima facie obvious to combine the antibodies and antibiotics to make a composition for the treatment of S. aureus. This is because it is prima facie obvious to "combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose..." See, MPEP § 2144.06 (quoting In re Kerkoven, 205 U.S.P.Q. 1069, 1072 (CCPA 1980)). Thus, the references render the identified claims obvious.

14. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Foster as applied to claim 1 above, and further in view of the teachings of Hook et al. (U.S. Patent 6,288,214) and Emery et al. (U.S. 6,027,736). This claim reads on monoclonal antibodies to the ClfA protein, wherein the antibodies are cross-reactive to other strains of the S. aureus. Foster has been described above. As indicated above, the reference teaches the use of the CLF33 polypeptide to make antibodies to the bacterium.

The specification of the present application teaches that the antibodies raised against the ClfA protein are cross-reactive. Page 12, lines 13-19. Further, the art recognizes the benefits of cross-reactive antibodies. For example, The Emery reference teaches that such antibodies are useful in conferring cross protection against multiple strains of a pathogen. Col. 2, lines 30-47. The art also provides some guidance as to how to make such antibodies. See, Hook et al., Cols 42-43. In particular, Hook teaches the use of core epitopic sequences of antigens to make cross-reactive antibodies. The reference teaches that the identification of such core sequences is known

in the art. Col 43, lines 21-25. Thus, it would have been obvious to those in the art to have made such cross-reactive anti-ClfA antibodies. The motivation to do so is the known effectiveness of such antibodies for affording protection against the multiple pathogenic strains for which they are reactive.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner
August 13, 2003

JAMES HOUSEL 8/24/03
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